Treatment of *Pneumocystis carinii* pneumonitis with trimethoprim-sulfamethoxazole

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Summary: ***Pneumocystis carinii*** **pneumonitis (PCP) is fatal in 90 to 100% of cases if no treatment is given. Trimethoprim-sulfamethoxazole (TMP-SMX) was used at one of two dosage levels in the treatment of 20 children with PCP and cancer. Of 14 patients treated with 20 mg TMP—100 mg SMX/kg•d, 12 recovered and 2 died. Treatment of the fatal cases and one of the patients who recovered was supplemented with pentamidine. When six patients were treated with 4 to 7 mg TMP—20 to 35 mg SMX/kg•d, four recovered and two died. Both fatal cases and one of the patients who recovered were also treated with pentamidine. There were no significant adverse effects from TMP-SMX.**

Résumé: ***Le traitement de la pneumonite à Pneumocystis carinii par le triméthoprime-sulfaméthoxazole***

La pneumonite à *Pneumocystis carinii* (PPC) a une issue fatale dans 90 à 100% des cas si elle n'est pas traité. Nous avons traité 20 enfants souffrant de PPC et de cancer au moyen du triméthoprime-sulfaméthoxazole (TMP-SMX) à une des posologies suivantes. Sur les 14 malades auxquels nous avons donné 20 mg de TMP et 100 mg de SMX par kg et par jour, 12 ont été guéris et 2 sont morts. Le traitement des cas ayant eu une issue fatale et un des malades qui ont guéri était complété par la pentamidine. Quant aux six malades qui ont été traités par la posologie comportant 4 à 7 mg de TMP et 20 à 35 mg de SMX par kg et par jour, quatre ont guéri et deux sont morts. Les deux cas fatals et un des malades qui ont guéri avaient reçu également de la pentamidine. La médication TMP-SMX n'a entraîné aucune réaction défavorable de quelque importance.

Pneumocystis carinii pneumonitis (PCP) is usually fatal in the immunosuppressed host if untreated.[1,2] Pentamidine isethionate is considered to be the drug of choice for the treatment of this infection. In a study of 41 children with PCP treated with pentamidine at St. Jude Children's Research Hospital, 68% recovered.[3] Evidence of nephrotoxicity was found in 17 (41%), adverse reactions at injection sites in 17 (41%) and hypoglucosemia in 11 (27%) of the patients. Similar side effects were recognized by others.[2,4] Response to therapy with pentamidine is slow and the drug is not commercially available in the United States. Therefore, a more effective, readily available and less toxic drug is needed for the treatment of PCP.

Recent studies in our laboratory have shown the combination of trimethoprim-sulfamethoxazole (TMP-SMX) to be effective in both the treatment and prevention of PCP in cortisone-treated rats.[5]

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Trimethoprim-sulfamethoxazole has been used extensively outside the United States for the treatment of bacterial infection and has recently become commercially available in this country. The pattern and relative incidence of adverse reactions are those expected from a sulfonamide of low toxicity. Analysis based on 20 million 20-dose courses of TMP-SMX therapy identified 2151 (0.01%) cases with adverse reactions.[6] Cutaneous sensitivity and gastrointestinal reactions constituted about 75% of the reported reactions.

We report here the efficacy of trimethoprim-sulfamethoxazole in the treatment of patients with PCP.

Method

With the availability of pentamidine, a drug of proved value for the treatment of PCP, clinical studies to evaluate a new drug of unproved efficacy demanded a compromise with the desired experimental design in order to provide for the safety and proper treatment of patients. Unrestricted randomization of consecutive cases between pentamidine and TMP-SMX might jeopardize the critically ill patient who received TMP-SMX should it not prove effective. Since the natural course of PCP is predictable and associated with a mortality rate of 90 to 100% if untreated,[1,2] we elected to initiate the clinical evaluation with a pilot study in which patients would be selected fairly early in the course of illness and with a provision for the addition of pentamidine if the disease progressed adversely. A prospective protocol was followed.

Selection of patients

The patients were required to meet the following qualifications: a respiratory rate greater than 30 but less than 60/min; clearly discernible pneumonitis by chest radiography; Pa_{O_2} values greater than 60 mm Hg while breathing room air; primary malignant neoplasm; *P. carinii* demonstrated in lung aspirate or biopsy specimen; and informed consent of parents.

Drugs

Trimethoprim-sulfamethoxazole (TMP-SMX): Two dosage levels of TMP-SMX were studied in two groups of patients. The lower dose provided 4 to 7 mg TMP and 20 to 35 mg SMX per kg daily in two equal doses administered orally at 12-hour intervals. The higher dose was 20 mg TMP and 100 mg SMX/kg•d in four equal doses administered at 6-hour intervals. The patients were treated for 14 days. The preparations used were tablets (80 mg TMP and 400 mg SMX per tablet) and a suspension (40 mg TMP and 200 mg SMX per 5 ml) supplied by Hoffmann-La Roche Limited.

Pentamidine isethionate: Pentamidine, obtained from the parasitic disease drug unit, National Center for Disease Control, was administered intramuscularly as a single daily dose in the amount of 5.0 mg/kg•d.

Indications for the addition of pentamidine

The following criteria were set forth and followed to determine if and when pentamidine would be added to the TMP-SMX regimen: an increase in the density or distribution of pulmonary infiltrates in chest radiographs plus one of the following—an increase in the respiratory frequency to more than 80/min over a 6-hour period; decrease in PaO_2 to 60 mm Hg or less at FiO_2 of 40 vol% on two consecutive readings at least 1 hour apart; persistence of fever and no change in pulmonary infiltrates after 1 week of TMP-SMX therapy; adverse side effects or uncontrollable toxic effects of the drugs; or any change in the course of the illness which indicated that the condition of the patient was in jeopardy.

Diagnostic lung aspiration

Specimens obtained by percutaneous transthoracic needle aspiration of the infected lungs were stained with Gomori's methenamine silver nitrate, toluidine blue O, polychrome methylene blue and Gram's stains and cultured for bacteria and fungi.

Cultures of the blood, urine, throat and stool were made for bacteria and fungi prior to the onset of antimicrobial therapy.

Radiographs

Chest radiographs were made daily during the 1st week and on days 9, 11, 13 and 16 of therapy.

Hematologic and biochemical studies

Patients were monitored with determinations of leukocyte, erythrocyte, reticulocyte and platelet counts; hemoglobin, hematocrit and mean corpuscular values; values of serum glutamic oxaloacetic transaminase (SGOT), blood urea nitrogen (BUN), bilirubin, total and fractional proteins, sodium, chloride, potassium, bicarbonate, calcium, phosphorus, alkaline phosphatase, immunoglobulins A, G and M, folic acid, arterial blood gases and pH; and urinalysis.

Trimethoprim and sulfamethoxazole serum levels

Sera for the determination of trimethoprim and sulfamethoxazole concentrations were collected before initiation of therapy and daily during the first 7 days and on days 9, 11 and 13 of treatment and also 1 day after the drugs were discontinued. Each day blood samples were taken immediately before and 2 hours after the 8 am dose of the drugs. Doses were given at 8 am and 8 pm for the low-dose group and at 8 am, 2 pm, 8 pm and 2 am for the high-dose group. Trimethoprim was measured by the spectrofluorometric method of Schwartz, Koechlin and Weinfeld[7] and sulfamethoxazole by the method of Bratton and Marshall.[8]

Results

Twenty patients were treated. The primary disease was acute lymphocytic leukemia in 14, acute myelocytic leukemia in 2, lymphosarcoma in 3 and rhabdomyosarcoma in 1 of the patients. Three of the children were in relapse and 17 were in remission at the time of PCP. Ages ranged from 7 months to 15 10/12 yr (median, 5 2/12 yr).

Signs or symptoms of PCP had been present from 1 to 14 days (median, 4 days) before treatment was started.

Pretherapy chest radiographs showed diffuse alveolar disease in all patients. In 16 of the children the disease was bilateral, invading all lobes. In four patients the pneumonitis was unilateral, but within 24 hours both lungs were involved.

Baseline arterial oxygen tension values, with patients breathing room air, were between 62 and 72 mm Hg in 14, between 73 and 83 mm Hg in 3 and between 84 and 92 mm Hg in 3 of the patients.

Low dosage

Six patients were treated with the lower dosage of 4 to 7 mg trimethoprim and 20 to 35 mg sulfamethoxazole/kg•d (Fig. 1). The children had been ill with fever or respiratory symptoms from 1 to 14 days (median, 5 days) before treatment was started. Three patients recovered without additional therapy. They were afebrile in 1 to 3 days, chest radiographs were normal in 3 to 5 days, and the PaO_2 values were greater than 85 mm Hg at room air by days 2 to 4 of therapy. One patient required three doses of pentamidine because of an increase in the respiratory rate to 92/min on day 3 of TMP-SMX therapy. The temperature was normal on day 3, chest radiographs were first normal on day 11, and the PaO_2 was greater than 85 mm Hg (at room air) by day 8 and thereafter.

Two patients became progressively worse and pentamidine was started on day 3 of treatment. One patient died 24 hours after the first dose of pentamidine. Although this patient also had *Pseudomonas aeruginosa* sepsis ante mortem, an autopsy revealed PCP to be the cause of death. The second patient died after 14 days of pentamidine and 19 days of TMP-SMX therapy. Permission for an autopsy was not given. The pneumonitis became progressively worse as seen by chest radiography. Despite assisted ventilation no improvement was noted in the blood gases and FiO_2 requirements progressively increased to 100 vol%.

One of the six patients had a transient maculopapular rash believed to be related to TMP-SMX.

High dosage

Fourteen patients were treated with the high dosage of 20 mg

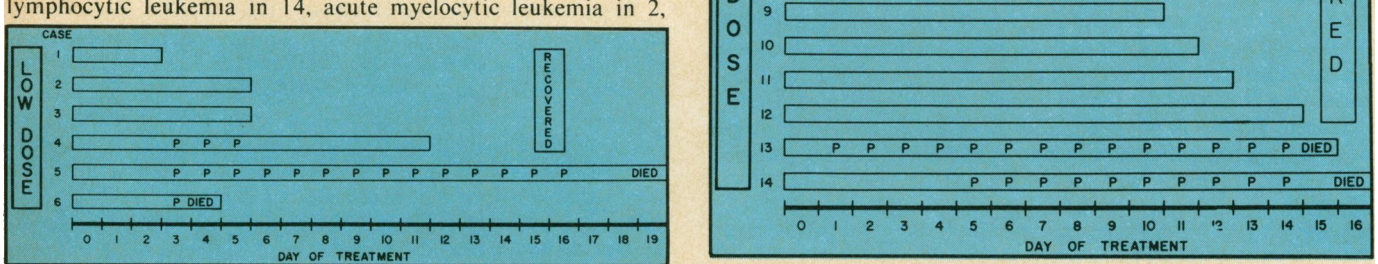

FIG. 1—Duration of pneumonitis determined from chest radiographs in 20 patients with *P. carinii* pneumonitis treated with TMP-SMX. P= days on which pentamidine was administered. Recovery is defined as normal chest radiograph, respiratory frequency less than 30/min, absence of symptoms, fever less than 38°C and PaO_2 of 85 mm Hg or more at room air. Left: Six patients treated with low dosage of 4 to 7 mg TMP + 20 to 35 mg SMX/kg•d for 14 days. Right: Fourteen patients treated with high dosage of 20 mg TMP + 100 mg SMX/kg•d for 14 days.

TMP—100 mg SMX/kg•d (Fig. 1). The children had been ill with fever or respiratory symptoms for 1 to 7 days (median, 4 days).

Eleven of the 14 patients recovered completely with TMP-SMX treatment alone. Defervescence occurred in 1 to 6 days (median, 3 days), chest radiographs were normal in 5 to 15 days (median, 8 days) and PaO_2 at room air was greater than 85 mm Hg by 1 to 9 days (median, 6 days) after the onset of TMP-SMX therapy.

Three of the 14 patients required the addition of pentamidine on days 1, 3 and 5, respectively, because of progressive pneumonitis. One patient recovered completely after 5 doses and two died after 10 and 15 doses of pentamidine, respectively. The terminal event of one fatal case was that of a tension pneumothorax and pneumomediastinum. At autopsy no *P. carinii* organisms could be found in the lungs. Histopathology of the lungs was compatible with that of oxygen toxicity. This patient had required 11 days of assisted ventilation and 6 days of FiO_2 over 90 vol%.

In the second fatal case the patient died on day 15. Pentamidine was started after the patient had been treated for 24 hours with TMP-SMX. The pneumonitis did not improve and respirator assistance was required from day 3 of therapy until death. At autopsy *P. carinii* pneumonitis of moderate severity was found associated with areas of extensive emphysema. In addition, there was extensive acute hemorrhagic pancreatitis with no apparent cause.

Three of the 14 patients had transient nausea and vomiting associated with TMP-SMX administration.

Adverse effects

No evidence of adverse effects from TMP-SMX was apparent from serial determinations of leukocyte count and differential, hemoglobin value, mean corpuscular values, platelet estimates, reticulocyte count, values of SGOT, BUN, serum electrolytes, folic acid, alkaline phosphatase, calcium and phosphorus, and urinalysis. One patient had a maculopapular rash and three had nausea and vomiting possibly caused by TMP-SMX. Discontinuation of the drugs was not necessary.

Course after recovery

The 16 patients who recovered have been observed from 1 to 13 months after termination of therapy. None has had evidence of recurrence of *P. carinii* infection.

Serum levels of TMP-SMX

The mean serum levels of TMP and SMX are shown in Fig. 2 for days 1, 3, 6, 9 and 13 of therapy. Although there were variations in values, as indicated by standard deviations, these were equally distributed among the patients studied and were not limited to individual patients. Drug concentrations in patients not responding to TMP-SMX were not different from those in patients who recovered.

Discussion

The natural course of PCP in the immunosuppressed host can be deduced from reports in which the diagnosis was established but the patients either received no treatment or were given drugs now known to be ineffective in treatment of this infection. In LeClair's survey of 107 cases of PCP in the United States occurring from 1955 through 1967, 102 patients (95%) died.[9]

Western, Perea and Schultz[2] reported the cases accumulated through the Center for Disease Control (CDC) from 1967 through 1970 and mentioned six patients in whom the diagnosis of PCP was made but pentamidine requested from the CDC was either not received or not administered. All of these patients died. In seven proved cases of PCP in which patients received either amphotericin B or no treatment, six died.[1] Comparison of the results of TMP-SMX therapy with the expected natural course of the infection strongly suggests that this drug combination is effective in the treatment of PCP. In the cortisone-treated rat model with PCP we found the mortality to be 36% in animals treated with TMP-SMX whereas 100% of the untreated controls died with PCP. Furthermore, animals treated prophylactically with TMP-SMX did not acquire the infection.[5]

A somewhat similar drug combination, pyrimethamine and sulfonamide, has been effective in the treatment of PCP in animals.[10] However, the limited clinical studies in man have produced equivocal results.[11-13]

The mechanisms by which TMP-SMX affects *P. carinii* can be inferred from studies that have been done with bacteria. Trimethoprim is a potent inhibitor of microbial dihydrofolate reductase, the enzyme responsible for the reduction of dihydrofolate to tetrahydrofolate.[14] Since trimethoprim binds to mammalian dihydrofolate reductase 50 000 times less than to the bacterial enzyme, a wide margin of safety exists with human usage. Sulfamethoxazole competitively inhibits the incorporation of para-aminobenzoic acid into dihydrofolate. It is reasonable to expect the drugs to have similar modes of action against *P. carinii*.

The dosage of 20 mg of trimethoprim and 100 mg of

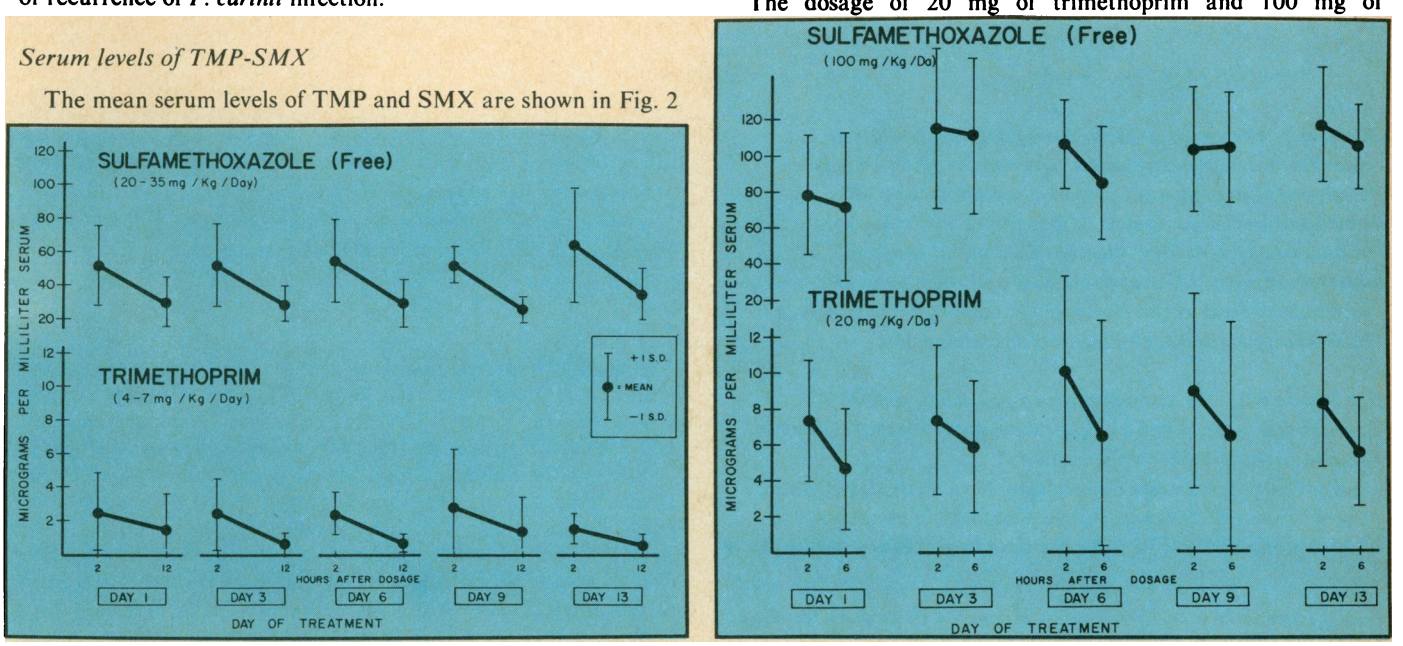

FIG. 2—Mean serum values of TMP and SMX determined during the 14-day course of treatment (± 1 SD). Left: Six patients receiving 4 to 7 mg TMP + 20 to 35 mg SMX/kg•d. Right: Ten patients receiving 20 mg TMP + 100 mg SMX/kg•d.

sulfamethoxazole/kg•d is superior to the lower dosage used in this study. Administration for a period of 14 days was adequate. Although recurrences have not occurred, the period of follow-up has not been adequate to permit valid conclusions. We have found in earlier studies that recurrence of the infection, or reinfection, usually occurs from 4 months to 1 year after recovery from the initial episode treated with pentamidine.[3,15]

Concomitant use of pentamidine and TMP-SMX for the treatment of PCP has not been studied. Since the mechanism by which pentamidine affects *P. carinii* is not known the possibility of synergism or antagonism with TMP-SMX cannot be predicted.

Emphasis must be placed on the fact that the cases in this pilot study were of mild to moderate severity and that critically ill patients were excluded. Furthermore, additional studies are required to compare the therapeutic efficacy of pentamidine with that of TMP-SMX. These studies can now be justified.

We have demonstrated clearly that TMP-SMX is effective in the treatment of PCP by comparing its effect with the expected natural course and the therapy is free of any significant adverse side effects.

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Antiplasmodial efficacy of 2,4-diaminopyrimidine-sulfonamide combinations, especially against chloroquine-resistant malaria

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Summary: This presentation deals with the historical development of the antifolate pyrimidines and related compounds, first as antimalarial substances and later as potent antibacterial agents. It describes the first quantitation of the combined action, through sequential blockade, of the substances with sulfonamides, and outlines the usefulness of the combinations in the therapy of normally sensitive and multiresistant strains of *Plasmodium falciparum*.

Résumé: *Efficacité antipaludéenne des associations de diamino-2,4-pyrimidine et de sulfonamide, surtout contre la malaria résistante à la chloroquine*

Le présent article fait l'historique de la mise au point des pyrimidines antifolates et de leurs dérivés, d'abort comme antipaludéens et, par la suite, comme bactéricides puissants. Il décrit les méthodes qui ont permis la première mesure quantitative de l'action combinée de ces substances avec les sulfonamides par bloquages successifs, et souligne l'utilité de ces associations dans le traitement des souches de *Plasmodium falciparum* normalement sensibles et polyrésistantes.

The successful development of antimalarial sulfonamides and pyrimidines dates from early in the history of effective antimicrobial chemotherapy. The demonstration of an antimalarial effect of sulfonamides in 1937 was followed shortly afterwards by the synthesis and testing of many pyrimidine derivatives for antimalarial activity. The reasons for choosing pyrimidine as a basis for molecular modification turned out, however, to be largely fallacious. Resemblance was sought with earlier antimalarial compounds of different chemical species based on a rather far-fetched analogy of sulfonamides as derivatives of analine, with a side-chain performing the same function as the basic side-chain of the older antimalarials. Pyrimidines were looked on favourably because they showed the characteristic of

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